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Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Post-market vigilance and introduction of the Database of Adverse Event Notifications

The TGA seeks information from a variety of sources, including spontaneous adverse event reports, when monitoring the safety of medicines and vaccines on the market. Information about adverse events (AEs) to medicines that have been reported to the TGA is now available to the public. Health professionals may receive enquiries from patients, who are encouraged to discuss any concerns with a health professional.

Medicine monitoring

When a medicine is first registered and made available in Australia, information about its safety and efficacy is usually only available from clinical trials. Clinical trials provide information about many of the possible risks associated with a medicine, but they do not detect all possible adverse effects, especially rare ones.

Monitoring the safety of medicines contributes to a better understanding of their possible adverse effects when they are used outside the controlled conditions of clinical trials.

The TGA regulatory processes aim to ensure that any risk associated with therapeutic goods is minimised and managed.

Analysis of AEs is one way that the TGA monitors the safety of medicines used in Australia.

Reporting of adverse events

The TGA encourages reporting of all suspected AEs to any medicine available in Australia, including prescription medicines, vaccines, over-the-counter medicines and complementary medicines.

An AE is any untoward medical occurrence in a patient administered a medicine but which does not necessarily have a causal relationship with the medicine. An AE can be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicine, whether or not it is considered to be related to the medicine.

Reporting of AEs complements other sources of safety information. The TGA is particularly interested in serious AEs, such as those that require or prolong hospitalisation; require a visit to the doctor; or result in death, disability, sequelae or birth defects.

It is not mandatory for health professionals to report AEs to medicines. However, the TGA gratefully receives a large number of reports from general practitioners, pharmacists, hospitals and allied health workers. Sponsors, who must report serious AEs, contribute about one-third of the reports.

Most of the states and territories have legislation mandating the reporting of adverse events following immunisation (AEFIs) to their respective health departments, who then report these to the TGA. The TGA encourages health professionals to check legislative requirements for reporting AEFIs with their state or territory health department.

What happens to your reports?

Each report is entered into the national database, which is regularly analysed by TGA staff to identify safety signals. When the TGA identifies a signal, it undertakes

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TGA Health Safety Regulation

a detailed evaluation to establish the possible role of a medicine in causing the AE.

TGA's response to a signal

A response to a signal is a regulatory action that the TGA undertakes to mitigate or minimise the risk identified. Actions could include alteration of product labelling; changes to the Product Information (PI); other changes to conditions of registration; communication of important benefit-risk information to relevant stakeholders; product suspension, cancellation or recall; an investigation of the manufacturing site; or a requirement to undertake a post-market study. Where the signal remains unclear, no regulatory action may be taken and the TGA continues to monitor the medicine.

The Database of Adverse Event Notifications

The TGA recently launched the Database of Adverse Event Notifications (DAEN), an online resource that provides community access to information about AEs to medicines that have been reported to the TGA. The DAEN can be found at www.tga.gov.au/daen.

The DAEN was launched in response to growing public demand for information about medicines and as part of TGA initiatives to be more transparent about its activities. Information in the DAEN is aimed to support the quality use of medicines in Australia and stimulate reporting of AEs.

Information

The DAEN includes AE information on prescription medicines, vaccines, over-the-counter medicines and complementary medicines reported to the TGA from 1971 to up to three months before the date of access. During this three month period, the TGA reviews the reports received and in some circumstances, especially where the report refers to a serious AE, seeks follow-up information from the reporter. The more complete the report is, i.e. where it contains concomitant medications and illnesses, investigations undertaken and timelines, the more useful it is for signal investigations and analyses.

The DAEN does not include information about medicines accessed via the special access, authorised prescriber, clinical trial notification or clinical trial exemption schemes, except where the AE report also includes a suspected general marketed medicine. The data do not include any personal information within the meaning of the *Privacy Act 1988*.

Searching facility

The DAEN provides users with a detailed explanation of the limitations to the data and search results.

There are optional advanced search criteria allowing users to narrow their search to specific AEs or to AEs within broad categories, for example cardiovascular or gastrointestinal disorders.

The DAEN provides users with the ability to view the search results in two formats – a medicine summary and a list of reports. The medicine summary groups reported adverse events together by broad categories. The list of reports provides the details of de-identified case reports.

What the DAEN means for health professionals

Users are advised not to use the database to evaluate the safety of a medicine, as it is not a substitute for medical advice. Users with concerns about their medication are encouraged to consult their doctor or health professional. In these cases health professionals are encouraged to advise patients that a report of an AE does not necessarily indicate there is a causal link between a medicine and an adverse outcome.

The DAEN reflects the TGA's commitment to improve community understanding of its role as a regulator in the health system and to enhance public trust in the safety and quality of therapeutic goods.

The TGA expects that the database will encourage more people to report problems experienced with medicines and so be better able to identify and respond to safety concerns.

Further information

More information, such as PIs and Australian Public Assessment Reports for prescription medicines (AusPARs), is available from the TGA website. When prescribing a new medicine, health professionals are encouraged to discuss the Consumer Medicine Information (CMI) with their patients and focus on the benefits and risks associated with the use of the medicine.

Reporting adverse events

The TGA relies on health professionals, manufacturers and suppliers, as well as consumers to report problems with medicines. This allows the TGA to identify and respond to emerging safety problems. For information on how to report see 'What to report' on page 163 or visit the TGA website.

MEDICINES SAFETY UPDATE

Lenalidomide (Revlimid) and second primary malignancy

The TGA reminds prescribers that lenalidomide (Revlimid) has been associated with an increased incidence of second primary malignancies in clinical trials. Prescribers should consider both the potential benefits and the risk of second primary malignancies, and screen patients for new cancers during treatment.

Lenalidomide is an immunomodulatory agent with anti-angiogenic and antineoplastic properties. In combination with dexamethasone, lenalidomide is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy. Lenalidomide is also indicated for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Evidence of risk with lenalidomide

In clinical trials of previously treated multiple myeloma, an increased incidence of second primary malignancy has been observed in patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to dexamethasone alone (1.38 per 100 patient-years).[1] These were mostly basal cell and squamous cell skin cancers, although solid tumours were also observed.

While lenalidomide is not approved for first-line treatment of multiple myeloma in Australia, in clinical trials of newly diagnosed multiple myeloma, a four-fold increase in the incidence of second primary malignancies has been observed in patients receiving lenalidomide (7.0%) compared to controls (1.8%).[2] These included cases of acute myeloid leukaemia, myelodysplastic syndrome and solid tumours in patients receiving lenalidomide in combination with melphalan or immediately following high-dose melphalan and autologous stem cell transplant. Cases of B-cell malignancies, including Hodgkin's lymphoma, were also observed in the clinical trials, in which patients received lenalidomide in the post-autologous stem cell transplant setting.

Information for health professionals

The following precaution is in the Product Information for lenalidomide:

> Second primary malignancies
>
> Based on a low number of cases, a numerical imbalance in second primary malignancies (comprising mainly of basal cell and squamous cell skin cancers) has been observed in clinical trials in previously treated multiple myeloma patients with lenalidomide/dexamethasone compared with placebo/dexamethasone.
>
> Both the benefit achieved with Revlimid and the risk of second primary malignancies should be considered before initiating treatment with the product. Physicians should also carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as appropriate.

If a decision is made to prescribe lenalidomide, health professionals should screen patients for new cancers during the course of the treatment.

REFERENCES

1. Dimopoulos MA, Richardson PG, Brandenburg N, Yu Z, Weber DM, Niesvizky R, et al. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood 2012;119:2764-7.
2. Celgene Corporation. Revlimid (lenalidomide). Health Cananda Product Monograph. Revised 2012.

Erratum: Accidental paracetamol poisoning

The Editor of MSU has become aware of an error in this article published in the August 2012 issue of MSU (vol 3; no 4, 2012). The TGA has referred back to the original source cited in the Lubel et al article in the Medical Journal of Australia in 2007.

The text should read "In a study of 662 patients with acute liver failure, 275 were cases of severe paracetamol-induced hepatotoxicity. 131 (48%) of these 275 cases were the result of an unintentional overdose and 19 (7%) of the 275 patients had not exceeded the recommended maximum daily dose of 4g". The correct reference for this paragraph is:

Larson AM, Polson J, Fontana RF, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-72.

The author and the editor of MSU regret this error.

MEDICINES SAFETY UPDATE

Kogenate: home use Factor VIII and filtration

Kogenate is a recombinant human antihaemophilic Factor VIII which is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital Factor VIII deficiency). It may also be used in patients with Factor VIII inhibitors (neutralising antibodies) who continue to respond to infused Factor VIII.

The use of the correct in-line filtration unit is of particular importance when infusing the reconstituted product. The TGA has been working with the company to update the instructions for reconstitution and administration in the Product Information to reflect the importance of using the filter provided with the product.

Particulate matter derived from incomplete mixing and debris from piercing the seal of the container may be present in the reconstituted product. The use of the filtration unit in the giving set supplied with the Kogenate ensures that any particles are removed from the infusion. The use of the provided giving set also reduces possible treatment failure as a consequence of human coagulation Factor VIII adsorption to the internal surfaces of some alternative infusion equipment.

Supply of Kogenate is through the Haemophiliac Centres, hospitals and individual haematologists. Pharmacists, haemophiliac nurses and medical practitioners are reminded of the importance of using the filtration unit in the giving set supplied with the Kogenate product.

As patients or their carers are responsible for the infusion of Kogenate when it is used prophylactically in the home setting, health professionals are reminded of the need to advise patients and their carers of the importance of using the giving set supplied with the Kogenate, which contains the correct in-line filtration unit.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Office of Product Review

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